REMARKS

I. STATUS OF THE APPLICATION

Claims 1 – 26 were filed in the original application. In response to the Restriction Requirement in the Office Action mailed April 10, 2006, the Applicants cancelled claims 1 – 26, 30, and 39 – 49, and added claims 50 – 87. In a previous Response to the Office Action of July 27, 2006 the Applicants cancelled claims 36, 61, 72 and 79, and amended claims 27, 28, 37, 53, 62, 69, 73, 75, and 80. Therefore, claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78, 80-87 are currently pending.

In the Final Office Action of December 20, 2006 there are 2 rejections. The currently pending rejections are:

1. Claims 27, 28, 32-34, 36-38, 50, 69, 70, 73-76, 80, 81, 84 and 85 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Hurst *et al.* (Rapid Comm. Mass Spectrom. (1996) 10:377-382.), (hereinafter "Hurst") in view of either Muddiman *et al.* (Anal. Chem. (1997) 69:1543-1549) (hereinafter "Muddiman") or Chen (U.S. Patent 6,613,509) (hereinafter "Chen").

2. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable Hoffman *et al.* (Arch. Virol. (2001) 146:2275-2289.) (hereinafter "Hoffman") in view of Koster (WO 98/20166) (hereinafter "Koster") and further in view of Muddiman or Chen.

II. STATUS OF THE REJECTIONS

Rejections under 35 U.S.C. 103(a)

A. Claims 27, 28, 32-34, 36-38, 50, 69, 70, 73-76, 80, 81, 84 and 85 are not obvious over Hurst in view of either Muddiman or Chen

In the Final Office Action of December 20, 2006 the rejection notes:

"It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Mass spectrometry base composition analysis methods of Muddiman or Chen in the mass spectrometry analysis method of Hurst . . ." (Final Office Action of December 20, 2006, page 5).

And:

"An ordinary practitioner would have been motivated to improve the Hurst method by the use of base composition analysis method of Muddiman in order to rapidly and accurately characterize the PCR products of Hurst down to the base composition level in order to confirm what sequence is present in the sample." (Final Office Action of December 20, 2006, page 5).

The Applicants respectfully disagree.

First, claim 36 was cancelled in the Response to Office Action of July 27, 2006, thereby rendering this rejection moot.

Second, a *prima facie* case of obviousness requires the United States Patent and Trademark Office to cite to a reference or references which a) disclose all the elements of the claimed invention, b) suggest or motivate one of ordinary skill in the art to combine the claim elements to yield the claimed invention, and c) provide a reasonable expectation of success should the claimed combination be carried out. Failure to

establish any one of these three requirements negates a finding of a *prima facie* case and, without more, entitles the Applicants to allowance of the claims in issue. (MPEP). The Applicants assert that the present rejection fails to meet these requirements.

1. The Rejection's References Does Not Provide a Suggestion or Motivation to Combine the Recited Elements

In the Final Office Action of December 20, 2006 the rejection notes:

> "An ordinary practitioner would have been motivated to use the Chen method to determine the base composition in order to permit sequence comparisons in an efficient and accurate way using the mass spectrometric method of Hurst combined with the mass spectrometric methods of Chen. Therefore, an ordinary practitioner, motivated to detect pathogens by Hurst, would have been motivated by both Muddiman and Chen to perform base composition analysis in order to obtain the benefits of increased speed, accuracy without the requirement to use gel electrophoresis or other sequencing methods." (Final Office Action of December 20, 2006, page 6).

The Applicants respectfully disagree. None of the cited references, alone or in combination, provide a motivation to combine the teachings as necessary to support the rejection. For example, the Hurst reference does not teach or suggest primers designed to hybridize to any pathogens other than *Legionella*. The Hurst reference provides no teaching or suggestion to make the rejection's combination with Muddiman or Chen. The Muddiman reference does not teach or suggest: a method for identifying a pathogen in a sample using the steps of amplifying a plurality of segments of nucleic acid of the pathogen with a plurality of primers (claim 27); a method of screening a biological sample to determine the presence or absence of pathogen wherein failure to produce one or more amplification products whose base compositions match known base compositions indicates the absence of the pathogen (claim 69); or a method of identifying one or more etiologic agents of disease in a sample (claim 75). Rather, Muddiman is

directed to PCR amplification and characterization of nucleic acids as "a viable method for monitoring microbial communities in soil and aquatic environments, allowing the progress of intrinsic or accelerated bioremediation efforts to be monitored on relatively short time scales." (Muddiman, pages 1543-1544).

Similarly, nothing in Chen teaches or suggests the rejection's combination. Chen uses a mass shift analysis to determine the number of nucleotides in an amplification product. Chen's analysis requires that 5 reactions are performed (one for each labeled oligonucleotide, and one for an unlabeled oligonucleotide), and then the mass shift with the label is subtracted from the mass shift without the label. The number of incorporated labeled residues is then calculated from the difference. Clearly, Chen does not teach or suggest the methods of base composition analysis of the claimed invention, and therefore does not, and cannot, provide motivation to an artisan or ordinary skill to make the rejection's combination.

In order to advance prosecution of this case, the Applicants hereby incorporate the enclosed declaration under 37 C.F.R. 1.132 by Dr. Seven Buchsbaum. In his declaration, Dr. Buchsbaum notes:

> "TIGER represents a completely novel approach which is not obvious in view of previously existing technologies. To my knowledge, no one ever previously proposed or disclosed that combining broad range priming of nucleic acid of bioagents with molecular mass measurements would be successful in rapid and accurate identification of bacterial and viral bioagents." (Declaration of Dr. Steven Buchsbaum, June 15, 2005, page 2).

Thus, contrary to the rejection's arguments, at the time the invention was made nothing in the cited references would lead one to use a plurality of primer pairs to amplify a plurality of segments of nucleic acid that undergo base composition determinations for the purpose of identifying a pathogen in a sample (claim 27). Nothing in the cited references would lead one to use one or more primer pairs for production of one or more amplification products whose base compositions match known base composition products to determine the presence or absence of a pathogen in a biological sample (claim

69). Similarly, nothing in the cited references would lead one to amplify a segment of nucleic acid from one or more etiologic agents of disease with one or more primer pairs to undergo base composition determinations for the purpose of identifying one or more etiologic agents of disease in a sample by comparison with known base compositions of known etiologic agents produced with the primer pairs (claim 75).

Correspondingly, the rejection fails to distinguish to which teachings in the cited art would guide the ordinary artisan to make the rejection's combinations. Moreover, in view of the limited focus of Hurst, Muddiman and Chen, the rejection fails to provide a teaching or suggestion to use additional element of the claims, for example, the broad range primers of claims 32 and 33.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

2. The Rejection's Combination of References Does Not Provide Reasonable Expectation of Success

The rejection's combination of references fails to provide a reasonable expectation of success in practicing the claimed invention. In order to advance prosecution of this case, the Applicants hereby incorporate the enclosed declaration under 37 C.F.R. 1.132 by Dr. Seven Buchsbaum. In his declaration, Dr. Buchsbaum notes:

> "Thus, the invention of the TIGER method produces results that would be unexpected by simply combining existing technologies such as general broad range priming and mass spectrometry." (Declaration of Dr. Steven Buchsbaum, June 15, 2005, page 2).

And:

> "In fact, an early internal review (funded by the DARPA director) carried out by JASON, an elite independent senior scientific advisory group that provides consulting services to the US government on matters of defense science and

technology, concluded that it was unlikely that development of the proposed methods would be successful. The unexpected success of the methods developed under the project was such that I nominated Ibis therapeutics for an award for best performance under a DARPA contract." (Declaration of Dr. Steven Buchsbaum, June 15, 2005, page 2).

And:

"I have also been pleased to observe that several independent commentaries and high visibility publications in prestigious journals have provided an indication that the TIGER methods are innovative, produce results that would be unexpected in light of prior technologies, satisfy a long-felt and unmet need and have great potential for commercial success." (Declaration of Dr. Steven Buchsbaum, June 15, 2005, page 3).

Hence, Dr. Buchsbaum's declaration provides evidence of the skepticism of experts as per MPEP 716.05. Weighing the power of the declaratory evidence as a consideration in the analysis of obviousness indicates that the claims are unobvious over the totality of the rejection's cited references.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

B. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are not obvious over Hoffman in view of Koster and further in view of Muddiman or Chen.

In the Final Office Action of December 20, 2006 the rejection notes:

"Further it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Mass spectrometry base composition analysis methods of Muddiman or Chen in the mass spectrometry analysis of Hoffman . . ." (Final Office Action of December 20, 2006, page 11).

The Applicants respectfully disagree.

1. The Rejection's References Does Not Provide a Suggestion or Motivation to Combine the Recited Elements

In the Final Office Action of December 20, 2006 the rejection notes:

"So an ordinary practitioner would have been motivated to detect the PCR products of Muddiman with the based composition Mass spectrometric approach of Koster since Koster teaches that Mass Spectrometry is accurate and can improve the speed, mass accuracy an precision of the analysis (see abstract, for example). (Final Office Action of December 20, 2006, page 11).

And:

"An ordinary practitioner would have been motivated to improve the Hoffman method by the use of the base composition analysis of Muddiman in order to rapidly and accurately characterize the PCR products of Hoffman down to the base composition level in order to confirm what sequence is present in the sample." (Final Office Action of December 20, 2006, page 11).

The Applicants respectfully disagree.

First, in *In re Sang Su Lee* the Court of Appeals for the Federal Circuit expressly prohibits substitution of the benefits of an invention (*i.e.*, rapid and accurate) for objective evidence of an invention's obviousness by the Patent and Trademark Office.[1]

Second, none of the cited references, alone or in combination, provide a motivation to combine the teachings as necessary to support the rejection. For example, the Hoffman reference does not teach or suggest primers designed to hybridize to any pathogens other than Influenza A virus. The Hoffman reference provides no teaching or

[1] *In re Sang Su Lee*, 277 F.3d 1338, 1341, USPQ2d 1430, 1433. (Fed. Cir. 2002).

suggestion to make the rejection's combination with Muddiman or Chen. Koster does not teach or suggest the identification of base compositions. The Muddiman reference does not teach or suggest: a method for identifying a pathogen in a sample using the steps of amplifying a plurality of segments of nucleic acid of the pathogen with a plurality of primers (claim 27); a method for characterizing a strain type of a pathogen using a plurality of primer pairs that hybridize to a plurality of segments of nucleic acid of the pathogen to obtain a plurality of amplification products, wherein one or more base compositions of the plurality of amplification products differs among different strain types of the pathogen (claim 53); a method of screening a biological sample to determine the presence or absence of pathogen wherein failure to produce one or more amplification products whose base compositions match known base compositions indicates the absence of the pathogen (claim 69); or a method of identifying one or more etiologic agents of disease in a sample (claim 75). Rather, Muddiman is directed to PCR amplification and characterization of nucleic acids as "a viable method for monitoring microbial communities in soil and aquatic environments, allowing the progress of intrinsic or accelerated bioremediation efforts to be monitored on relatively short time scales." (Muddiman, pages 1543-1544).

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In order to advance prosecution of this case, the Applicants hereby incorporate the enclosed declaration under 37 C.F.R. 1.132 by Dr. Seven Buchsbaum. In his declaration, Dr. Buchsbaum notes:

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Thus, contrary to the rejection's arguments, at the time the invention was made nothing in the cited references would lead one to use a plurality of primer pairs to amplify a plurality of segments of nucleic acid that undergo base composition determinations for the purpose of identifying a pathogen in a sample (claim 27). As well, nothing in the cited references would lead one amplify nucleic acid of a pathogen with a plurality of primer pairs that hybridize to a plurality of nucleic acid segments to obtain a series of base compositions that characterize different strain types of the pathogen (claim 53). In turn, nothing in the cited references would lead one to use one or more primer pairs for production of one or more amplification products whose base compositions match known base composition products to determine the presence or absence of a pathogen in a biological sample (claim 69). Similarly, nothing in the cited references would lead one to amplify a segment of nucleic acid from one or more etiologic agents with one or more primer pairs to undergo base composition determinations for the purpose of identifying one or more etiologic agents in a sample by comparison with known base compositions of known etiologic agents produced with the primer pairs (claim 75).

Correspondingly, the rejection fails to distinguish to which teachings in the cited art would guide the ordinary artisan to make the rejection's combinations. Moreover, in view of the limited focus of Hoffman, Koster and Muddiman or Chen, the rejection fails to provide a teaching or suggestion of additional elements of the claims, for example, the broad range primers of claims 32 and 33, or a method of detecting the unknown etiologic agents of claim 87. To the contrary, Hoffman, Koster and Muddiman or Chen require *a priori* knowledge of nucleic acid sequences.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

3. The Rejection's Combination of References Does Not Provide Reasonable Expectation of Success

The rejection's combination of references fails to provide a reasonable expectation of success in practicing the claimed invention. In order to advance prosecution of this case, the Applicants hereby incorporate the enclosed declaration under 37 C.F.R. 1.132 by Dr. Seven Buchsbaum. In his declaration, Dr. Buchsbaum notes:

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> "In fact, an early internal review (funded by the DARPA director) carried out by JASON, an elite independent senior scientific advisory group that provides consulting services to the US government on matters of defense science and technology, concluded that it was unlikely that development of the proposed methods would be successful. The unexpected success of the methods developed under the project was such that I nominated Ibis therapeutics for an award for best performance under a DARPA contract." (Declaration of Dr. Steven Buchsbaum, June 15, 2005, page 2).

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potential for commercial success." (Declaration of Dr. Steven Buchsbaum, June 15, 2005, page 3).

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In view of the above, the Applicants respectfully request that this rejection be withdrawn.

III. DOUBLE PATENTING

Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over particular claims of numerous co-pending applications. Upon indication of otherwise allowable subject matter, the Applicants will consider the filing of a Terminal Disclaimer.

CONCLUSION

All grounds of rejection of the Final Office Action of December 20, 2006 have been addressed, and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

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